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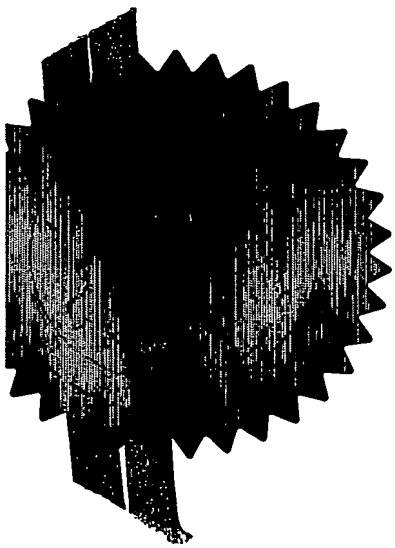

Signed Andrew Gersey

Dated 29 December 2004

Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference GBP290109

2. Patent application number
(The Patent Office will fill in this part)
0327908.0

3. Full name, address and postcode of the or of each applicant (underline all surnames)

NeuroPharma, S.A., 02DEC03 E856510-2 D10176
Avda. de la Industria, 52 P01/7700 0.00-0327908.0
Tres Cantos
28760 Madrid
Spain

8670754001

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation Spain

4. Title of the invention GSK-3 Inhibitors Isolated from Marine Organisms

5. Name of your agent (if you have one)
"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Marks & Clerk
66-68 Hills Road
Cambridge
CB2 1LA

Patents ADP number (if you know it) ~~18001~~ 7271125003.

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months

Country	Priority application No (if you know it)	Date of filing (day / month / year)

7. Divisionals, etc: Complete this section only if this application is a divisional, application or resulted from an entitlement dispute

Number of earlier application	Date of filing (day / month / year)

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? Yes
(Answer 'Yes' if:
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	0
Description	12
Claim(s)	4
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for preliminary examination and search (Patents Form 9/77)	1
Request for substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) Marks & Clerk Date: 2 December 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Cambridge Office
01223 345520

DUPLICATE

GSK-3 INHIBITORS ISOLATED FROM MARINE ORGANISMS

FIELD OF THE INVENTION

The present invention relates to GSK-3 inhibitors, and in particular to GSK-3 inhibitors isolated from marine organisms. The inhibitors are of use for treating Alzheimer's disease and other conditions.

BACKGROUND OF THE INVENTION.

Alzheimer's disease is characterized by the development of senile plaques and neurofibrillary tangles, which are associated with neuronal destruction, particularly in cholinergic neurons. Neurofibrillary tangles are structures formed by paired helical filaments (PHFs). They are comprised mainly of microtubule-associated protein (MAP) tau in an abnormally hyperphosphorylated state. Such aberrant phosphorylation of tau, determined by the effects of different protein kinases and phosphatases, appears to compromise on its ability to bind to and stabilise microtubules and this may contributes to AD pathology. Thus, the blockade of this hyperphosphorilation step may be a prime target at which to interrupt to pathogenic cascade.

The selective inhibitors of tau kinases might be new effective drugs for the treatment of AD. The search for tau kinases inhibitors is a field of a great interest. Tau can be phosphorilated by several prolines-directed kinases (PDKs) and non-PDKs. However in AD the extra role of any of this kinases in the abnormal hyperphosphorylation of tau is not yet understood and to date, the activity of these kinases has not been found to be up-regulated. There is no doubt that GSK-3β is an in vivo kinase in the brain. These findings open the gate to the use of GSK-3β inhibitors as therapeutical agents in treatment of AD.

GSK-3 is involved not only in neurodegenerative diseases as Alzheimer's disease, but also in diabetes type II, cancer, inflammation process and some other unmet disorders.

The oceans are the source of a large group of structurally unique natural products that are mainly accumulated in invertebrates such as sponges, tunicates, bryozoans, and mollusc [Burkhard Haefner, Drug Dis. Today. 2003,8,2,536-544]. Several of these compounds show pronounced pharmacological activities and are interesting candidates for new drugs in several areas of treatment [DJ. Newman, GM.Cragg, KM.Snader, J.Nat.Prod. 2003, 66, 1022-1037]. Once again sponges have provided more marine natural products than any order phylum, due in part to their propensity to produce bioactive metabolites [J.Faulkner, Nat.Prod.Rep. 2002,19,1-48].

At the moment few marine compounds are known as GSK-3 inhibitors: hymenialdisine [Meijer, L. *et al.* Chem.Biol. 2000, 7, 51-63] has been isolated from marine organisms.

SUMMARY OF THE INVENTION

In an effort to find selective inhibitors of GSK-3β, we have investigated the marine sponge *Ircinia sp.* [G.Alfano, G.Cimino and S. De Stefano.Tetrahedron. 1972, 28, 333]. In the course of our research, we found that isopropanolic extracts from sponges of genus *Ircinia* (species *dendroides, variabilis* and *oros*) showed potent inhibition of GSK-3β. Fractionation and purification of active components from these extracts, guided by a GSK-3 inhibition assay, resulted in the isolation of terpenoids as new GSK-3 inhibitors with potential use as therapeutic agents. Synthetic analogues can then be designed.

According to the present invention, we provide organic solvent extracts of the sponge *Ircinia sp.*, and specially *Ircinia dendroides, Ircinia variabilis* and *Ircinia oros*, which show activity as potent GSK-3 inhibitors; the furanoterpenoids of formula I either isolated from these extracts or synthetically prepared, which also show activity as potent GSK-3 inhibitors, especially Palinurin (1); and novel furanoterpenoids of formula II, which also show activity as potent GSK-3 inhibitors, especially Tricantin (2). These compounds are useful in the treatment of diseases in which GSK-3 is involved, mainly neurodegenerative diseases as Alzheimer's disease, and tauopathies (Corticobasal degeneration, Pick's disease, supranuclear palsy, etc), bipolar disorders, diabetes type II, hyperproliferative diseases as

cancer, displasais or metaplasias of tissue, psoriasis, arteriosclerosis or restenosis, and chronic inflammatory processess.

For example, we provide compounds of formula (I) or (2), pharmaceutical compositions which contain such a compound and a pharmaceutically acceptable carrier, methods of treatment which employ such compounds or compositions, processes for preparing pharmaceutical compositions, and the use of the compounds in the preparation of medicaments for use in the treatment methods. The pharmaceutical compositions, also referred to as medicaments, may be designed for oral administration as solid unit doses using conventional pharmaceutical auxiliary materials.

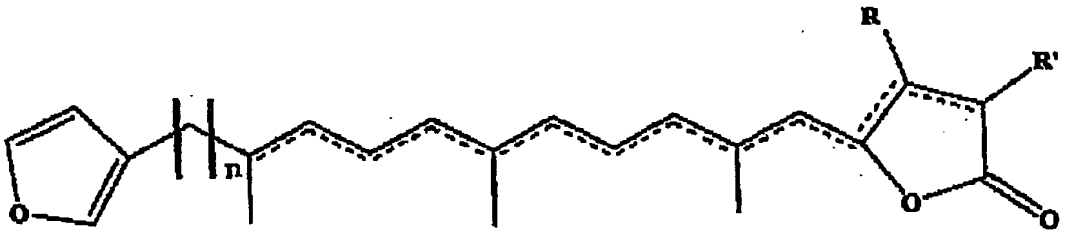
DETAILED DESCRIPTION OF THE INVENTION

Some sesterterpenes isolated from the sponge *Ircinia sp.* display a wide range of bioactivities, including cytotoxicity [Hamad H. Issa, Junichi Tanaka, Tatsuo Higa, J. Nat. Prod. 2003, *66*, 251-254], action as protein kinase inhibitor [Malcolm S. Buchanan, Annette Edser, J. Nat. Prod. 2001, *64*, 300-303] and antibiotic effect [John Faulkner, Tetrahedron Lett. 1973, *39*, 3821-3822]. Palinurin has been described as an anti-inflammatory and antibacterial compound [M.T.Hamann, J.Org.Chem.1999, 64,1258-1260].

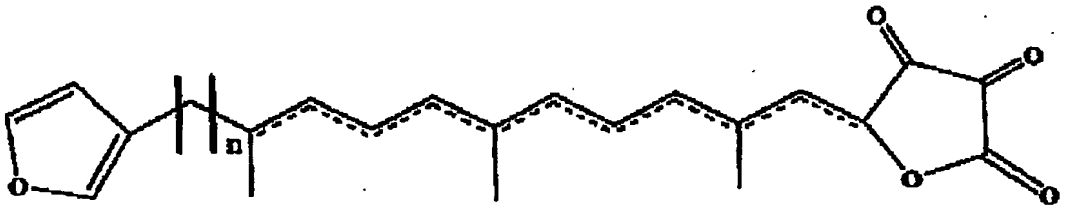
The present inventors have discovered, after thorough research, that organic solvent extracts, in particular the isopropanolic extracts, of the *Ircinia sp.*, in particular *Ircinia dendroides*, *Ircinia variabilis* and *Ircinia oros* collected from the Mediterranean Sea, showed potent inhibition of GSK-3β (90% of inhibition at 50 mg/ml).

The isopropanolic extract was partitioned between water and diethyl ether, and the organic layer was where the inventors found the inhibition of GSK-3β.

The purification of this fraction yielded the isolation of different compounds within the general formulae I and II.



FORMULA I



FORMULA II

where:

n is 0, 1, 2, or 3

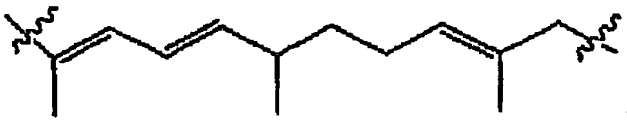
the bonds shown with the dashed lines are saturated, or unsaturated with one or more double bonds;

R, and R' are independently selected from hydrogen, alkyl, aryl, -OH, -OR", -SH, -SR", -NH_2, -NHR", =O, =NH, =NR";

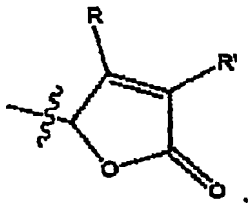
R" is independently selected from alkyl, aryl.

Preferably n is 3.

Preferably the carbon chain shown with the dashed line is saturated with carbon-carbon bonds (sp^3C-sp^3C) or unsaturated with one or more double bonds which are E-double carbon-carbon bonds (sp^2C-sp^2C), or Z- double carbon-carbon bonds (sp^2C-sp^2C). In particular for the carbon chain (excluding the ring) it is preferred to have two or more double bonds , especially two double bonds which are conjugated. Most preferred is to have double bonds giving the partial structure:



Furthermore, in the substituted tetrahydrofuran ring of formula (I), the preferred structure is:



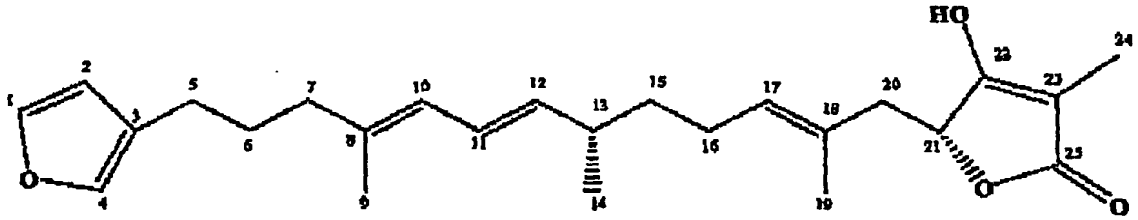
Preferably R is –OH or =O.

Preferably R' is =O or methyl.

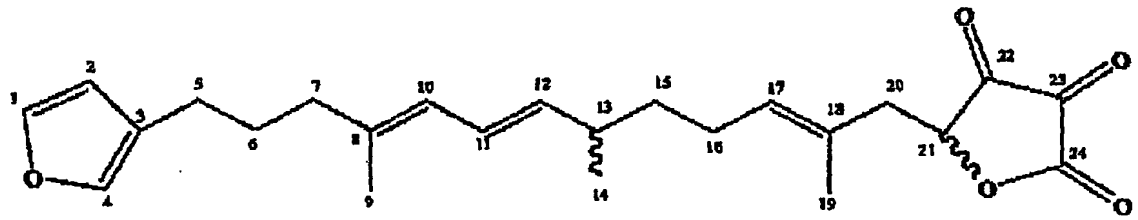
Alkyl groups preferably have 1 to 6 carbon atoms, more preferably 1 to 3 carbon atoms, such as methyl, ethyl or propyl.

Aryl groups preferably are phenyl or naphthyl.

Chemical elucidation of two of the compounds isolated from *Irinia sp.* revealed structures 1 and 2. These furanosesquiterpenoids detivatives showed potent inhibition on GSK-3.



Compound 1



Compound 2

Compound 2 is a new chemical structure not reported until date.

Such compounds, and the other compounds of the general formulae (I) and (II), can be prepared by synthesis.

The present invention is in particular directed to the use of the extracts and compounds obtained from the marine organism *Ircinia sp.* in the treatment of diseases in which GSK-3 is involved, as well as to the novel compounds of general formula II, in particular compound 2, isolated from the marine organism *Ircinia sp*

EXAMPLES OF THE INVENTION

1. Activity of the Compounds of the Invention:

1.1. Experimental procedures

1.1.1. GSK3ß inhibition

Recombinant human glycogen synthase kinase 3ß was assayed in MOPS 8 mM pH7.3, EDTA 0.2 mM, $MgCl_2$ 10 mM and sodium orthovanadate 0.25 mM in the presence of 62.5 µM of Phospho-Glycogen Synthase Peptide-2 (GS-2), 0.5 µCi γ-^{33}P-ATP and unlabelled ATP at a final concentration of 12.5 µM. The final assay volume was 20 µl. After incubation for 30 minutes at 30 °C, 15 µl aliquots were spotted onto P81 phosphocellulose papers. Filters were washed four times for at least 10 minutes each and counted with 1.5 ml of scintillation cocktail in a scintillation counter.

Marine extracts and fractions were routinely tested at a single concentration of 25 µg/ml whereas isolated compounds Palinurin and Tricantin IC50 values were calculated analyzing inhibition curves by non-linear regression using GraphPad Prism.

1.1.2. Inhibition of tau phosphorylation

Human neuroblastoma SHSY5Y cells were seeded in 96-well plates (25000 cells/well) in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum. One day later, cells were treated with samples for 24 h at 37°C. After treatment, cultures

were washed with phosphate-buffered saline and lysed for 30 min at 4°C in 120 µl of extraction buffer (10 mM Tris-HCl, pH 7.4, 100 mM NaCl, 1 mM EDTA, 2 mM Na_3VO_4, 1% Triton X-100, 10% glycerol, 0.1% SDS, 0.5% Sodium deoxycholate, 1 mM PMSF and a protease inhibitor cocktail.

The quantitative determination of phosphorylated human Tau was made taking 40 µl of the cell lysate and using a phosporylation-specific antibody against Tau [pS396] in a sandwich ELISA. Tau phosphorylation was estimated by measuring of absorbance at 450 nm in a microtiter plate reader.

In addition to tau phosphorylation assays, quantification of cell death and cell lysis was made by measuring LDH release. For the quantitative determination of cell survival, 40 µl of the cell lysate were incubated with an equal volume of reaction mixture at room temperature for 20-30 min. The measure of absorbance was made in a microtiter plate reader with 490-492 nm filter.

1.2. Biological activity

1.2.1. GSK3β inhibition

Different *Ircinia dendroides* extracts were tested at concentrations ranging from 5 to 50 µg/ml on the *in vitro* GSK3β assay. In these assay *Ircinia dendroides* extracts inhibit recombinant human GSK3 at concentractions over 15 µg/ml.

Kinetic analyses for isolated compounds were performed and the results show that Tricantin inhibits recombinant human GSK3β with an IC50 value of 7.5 □M, whereas Palinurin shows an IC50 valne of 4.5 µM.

In order to investigate the mechanism of inhibition of GSK3β by Palinurin, several kinetic experiments were performed varying both ATP and inhibitor concentrations. Preliminary experiments with Palinurin suggest that it might act as a non ATP-competitive inhibitor.

1.2.2. Inhibition of tau phosphorylation

Different *Ircinia dendroides* extracts were tested at concentrations ranging from 5 to 50 µg/ml on the *in vivo* phosphorylation assay. In these assay *Ircinia dendroides* extracts inhibit tau phosphorylation at concentractions over 50 µg/ml.

When assayed on the tau phosphorylation cellular assay, both Palinurin and Tricantin showed significant inhibition at a concentration of 200 µM.

2. Physical Properties of the Compounds of the Invention:

The chemical structure elucidation of the compounds were performed in basis to their spectrospical (IR, ES+, UV, ^{1}H-NMR and ^{13}C-NMR) data together with the results of bidimensional NMR experiments, both homonuclear, such COSY and NOESY pulse sequences, and hetereonucleat experiments such HMQC and HMBC pulse sequences.

The IR, ES+, UV, ^{1}H-NMR and ^{13}C-NMR spectrum of compound 1 showed the same bands of absorptions and signals (chemical shifts and coupling constants) than those was described by G. Alfano in 1979 as Palinurin.

So, here we described Palinurin as a potent GSK-3 inhibitor.

Compound 2 showed the same [M+H]+ ion at m/z 399 and the UVλ_{max} at 241nm that compound 1.

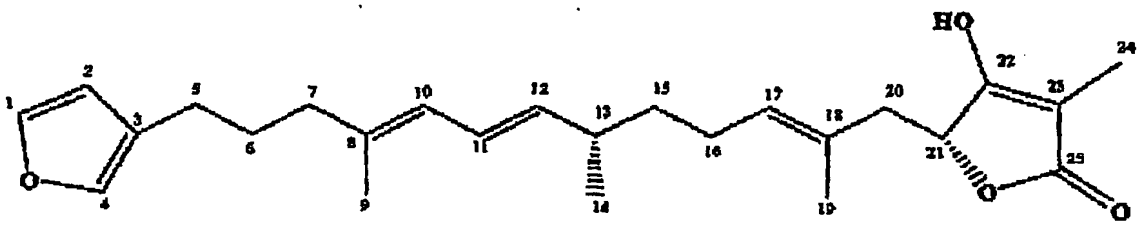
The IRν_{max} spectrum of Compound 2 showed one absorption band at 1724cm^{-1} attributable to carbonyl group while the band at 1756cm^{-1} attributable to double bond groups that appeared in Compound 1 is not shown in IR spectrum of 2.

The ^{1}H-NMR spectrum of compound 2 (Table 1) was almost identical to that of compound 1, with the exception that the oxamethynic proton (CH-21) which appeared in the spectrum of 1 at δ 4.8 ppm were replaced in 2 by a signal downfield at δ 4.38 ppm. The signal corresponding to the CH_3-24 of 1 which appeared at δ 1.64 ppm were disappeared in the spectrum of 2. This first evidence led to the suggestion that the change

was being in the tetronic acid residue, and it was confirmed when compared the ^{13}C-RMN chemical shifts of compounds 1 and 2.

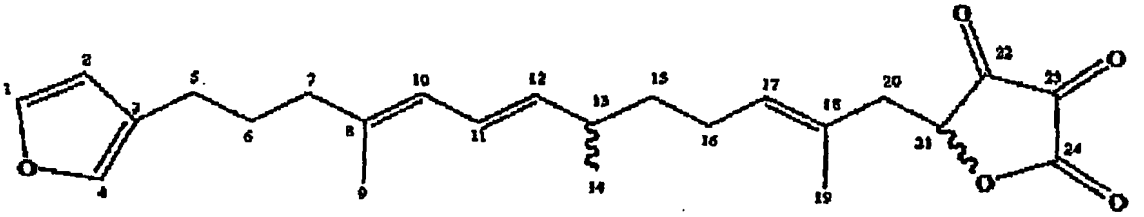
The carbon signal of CH_3-24 was also not observed in compound 2, and the chemical shifts of C-21, C-22 and C-23 was changed respected to Compound 1 (see table 1). The two carbon atoms C22 and C23 appeared at the same chemical shift δ 177.92 ppm than C24, this fact allowed us to assign the three carbonyl groups for our novel compound, these evidences led to the suggestion of structure 2. As this new compound was isolated in Tres Cantos, we have named it Tricantin

The shielded of C-21 is due to the anisotropy environment of carbonyl group in C-22 and the differences in chemical shifts of C-22 and C-23 were due to the presence of two new carbonyl groups. The structure of compound 2 was confirmed using a commercial compound (dehydroascorbic acid) as reference, in which we could observed that the three carbonyl groups appeared at the same chemical shifts as our novel compound.
The stereochemistry of Tricantin is not yet assigned.



Compound 1

Palinurin



Compound 2

Tricantin

Table 1

	Palinurin		Tricantin	
Atom	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR
1	7.36(s)	143.90 CH	7.38(s)	144.01 CH
2	6.28(s)	111.97 CH	6.29(s)	111.98 CH
3		126.31 C		126.38 C
4	7.23(s)	140.12 CH	7.25(s)	140.18 CH
5	2.39(t)	25.30 CH_2	2.38(t)	25.29 CH_2
6	1.70(m)	29.52 CH_2	1.69(m)	29.56 CH_2
7	2.06(t)	40.43 CH_2	2.10(t)	40.43 CH_2
8		136.80 C		136.80 C
9	1.71(s)	17.27 CH_3	1.71(s)	16.57 CH_3
10	5.75(d)	126.71 CH	5.77(d)	126.71 CH
11	6.20(dd)	126.69 CH	6.21(dd)	126.69 CH
12	5.38(dd)	139.09 CH	5.38(dd)	139.12 CH
13	2.20(m)	37.98 CH	2.20(m)	37.99 CH
14	0.98(d)	21.63 CH_3	0.98(d)	21.51 CH_3
15	1.31(m)	38.19 CH_2	1.31(m)	38.30 CH_2
16	2.00(q)	26.99 CH_2	2.00(q)	27.01 CH_2
17	5.24(t)	130.20 CH	5.23(t)	129.48 CH
18		130.63 C		131.89 C
19	1.71(s)	16.68 CH_3	1.71(s)	16.38 CH_3
20	2.62(d), 2.20(m)	42.53 CH_2	2.46(d), 2.20(m)	45.81 CH_2
21	4.76(d)	79.20 CH	4.21(dd)	70.84 CH
22		177.80 C		177.92 C
23		96.80 C		177.92 C
24	1.64(s)	6.11CH_3		177.92 C
25		177.60 C		

3. Origin of the Preferred Compounds of the Invention

Although the isolation described above of the compounds was conducted from *Ircinia dendroides* organic solvent extract, we have identified by HPLC/MS method the same compounds in several samples of other *Ircinia* species as *Ircinia variabilis* and *Ircinia oros*.

EXPERIMENTAL SECTION

Animal material

The sponge was collected in 2000 at Menorca sea (Spain). The sponge forms irregular straplike branches, the surface is conculose with fine protruding fibers, and it is flexible and very difficult to tear. The sponge is deep brownish-green in life and cream in preservative. The skeleton consists of large yellow platelike fibers with embedded detritus, and the sesohyl is permeated with distinctive sponging filaments.

The sample is *Ircinia dendroides* (Polejaeff) (ordet Dictyoceratida, family Irciniidae) first described from the Philippines. A voucher specimen has been deposited of the Natural History Museum, London, U.K. (BMNG 1992.10.1.1).

Extraction and Isolation

A sample of frozen sponge (300gr wet weight) was cut into small pieces (2cm) and triturated, the marine material was extracted with isopropanol (1.5L x 2). After decantation, the combined extracts were concentrated to give a brown solid (5.1gr) and partitioned between diethylether and water. The organic layer was concentrated to give a brown oil (1.8gr). The oil was chromatographed on silica gel with a stepwise gradient solvent system: DCM/ MeOH (100:1), DCM/ MeOH (75:1), DCM/ MeOH (50:1), DCM/ MeOH (25:1). Firstly, compound 1 (*Palinurin*) was isolated after this chromatography purification and the compound 2 (*Tricantin*) was isolated employing HPLC (RP-18, ACN-H_2O) separation.

Compound 1 has been previously described [G.Alfano, G.Cimino and S. De Stefano. Experientia.1979, 35, 1136-1137] .

Compound 2:

pale brown oil (1.8mg);

UVλ_{max}: 241nm,

IRν_{max} : 2927, 2856, 1724 cm^{-1},

ES+(20eV)M/z = 399(M+H).

^{1}H-NMR (CD_3OD, 400MHz, δ ppm): 7.38 (brs, 1H), 7.25 (brs, 1H), 6.29 (brs, 1H), 6.21 (dd, 1H, *J*=8Hz, *J*=15Hz), 5.77 (d, 1H, *J*=8Hz), 5.38 (dd, 1H, *J*=8Hz, *J*=15Hz), 5.23 (t, 1H, *J*=7Hz), 4.21 (dd, 1H, *J*=4.7Hz, *J*=8.4Hz), 2.46 (dd, 1H, *J*=4.7Hz, *J*=13.5Hz), 2.38 (t, 2H, *J*=7.6Hz), 2.30 (dd, 1H, *J*=8.4Hz, *J*=13.5Hz) 2.20 (m, 1H), 2.10 (t, 2H, *J*=7.6Hz), 2.00 (q, 2H, *J*=7Hz), 1.71 (s, 3H),1.69 (m, 2H), 1.68 (s, 3H), 1.31 (m, 2H), 0.98 (d, 3H).

^{13}C-NMR (CD_3OD, 100MHz, δ ppm): 178.0, 144.0, 140.1, 139.1, 136.8, 131.9, 129.4, 126.7, 126.6, 126.3, 11.9, 70.92, 45.8, 40.4, 38.3, 37.9, 30.8, 29.5, 27.0, 25.2, 21.5, 16.5, 16.7.

Materials and methods

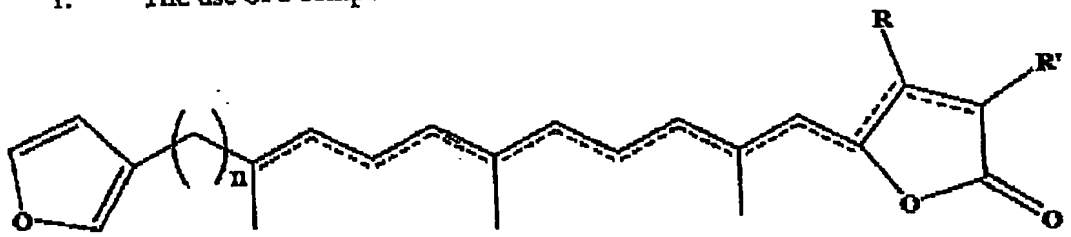
HPLC was perform with a symmetry C18 (4.6x150mm, 3.5µm) column using a Waters Alliance 2695 with a 2996 photodiode array and ZQ2000 mass spectrometer used for the analytical separation and for UV and mass determination. The gradient used for the elution was 0-5 min 80 % A: 20%B; 5-40 min 100%B; 40-45 min 100%B; 45-46 min 80%A: 20%B (A= H_2O 0.1% HF; B=AcN 0.1%HF).

IR Spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

^{1}H, ^{13}C, NMR spectra were recorded on a Varian AS 400 spectrometer in CD_3OD using the solvent as a reference standard (^{1}H, 4.87, 3.31, and ^{13}C, 49.1). ^{1}H, ^{13}C, COSY, HSQC, HMBC, NOE and DEPT spectra were obtained using standard Varian pulse sequences.

CLAIMS

1. The use of a compound of the formula:



FORMULA I

where:

n is 0, 1, 2, or 3

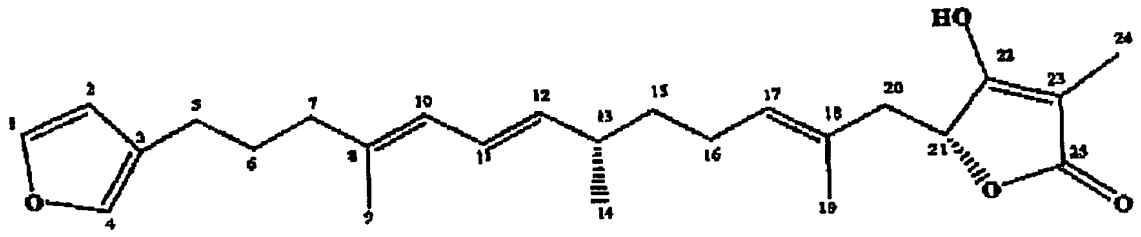
the bonds shown with the dashed lines are saturated, or unsaturated with one or more double bonds;

R, and R' are independently selected from hydrogen, alkyl, aryl, -OH, -OR", -SH, -SR", -NH_2, -NHR", =O, =NH, =NR";

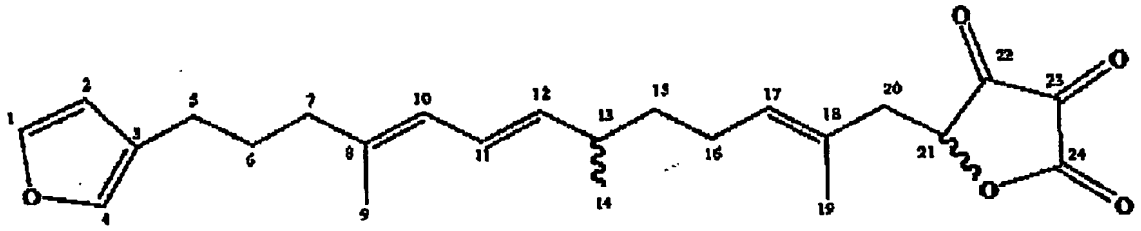
R" is independently selected from alkyl, aryl,

in the preparation of a medicament for the treatment of a disease requiring a GSK-3 inhibitor.

2. The use according to claim 1, wherein the compound is compound 1 or compound 2:



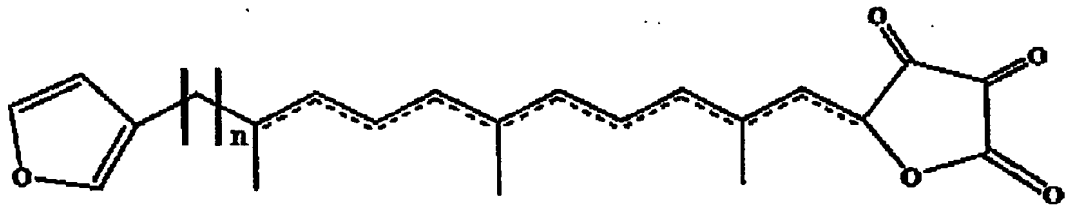
Compound 1



Compound 2.

3. The use according to claim 1, wherein the disease is Alzheimer's disease, or a tauopathy (Corticobasal degeneration, Pick's disease, supranuclear palsy, etc), bipolar disorder, diabetes type II, hyperproliferative disease such as cancer, displasais or metaplasias of tissue, psoriasis, arteriosclerosis or restenosis, or chronic inflamntatory process.

4. A compound of the formula:



where

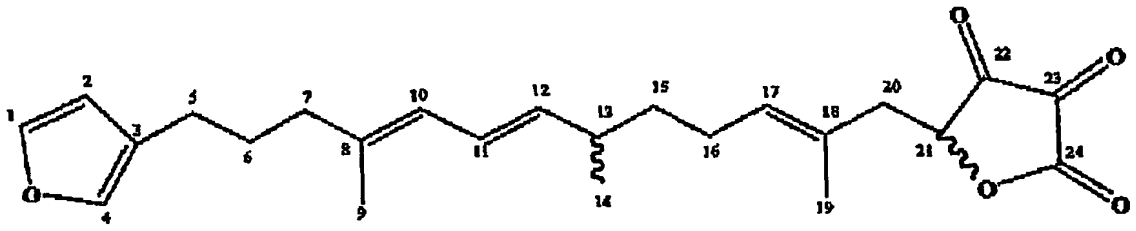
n is 0, 1, 2, or 3

the bonds shown with the dashed lines are saturated, or unsaturated with one or more double bonds;

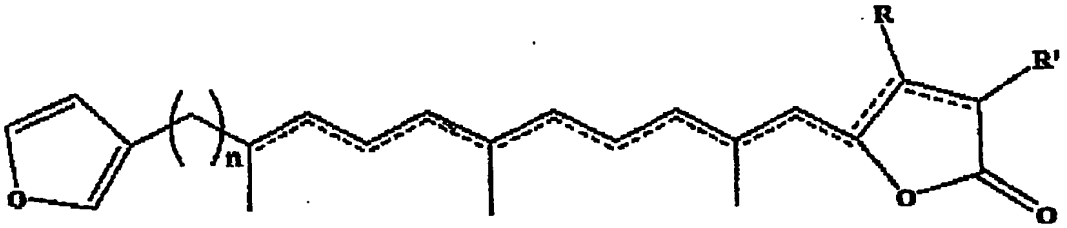
R, and R' are independently selected from hydrogen, alkyl, aryl, -OH, -OR", -SH, -SR", -NH_2, -NHR", =O, =NH, =NR";

R" is independently selected from alkyl, aryl.

5. A compound according to claim 4, of the formula:



6. A pharmaceutical composition for use as a GSK-3 inhibitor comprising a compound of the formula:



FORMULA I

where:

n is 0, 1, 2, or 3

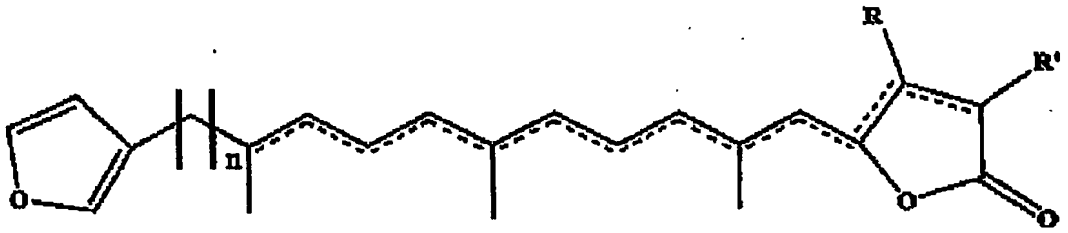
the bonds shown with the dashed lines are saturated, or unsaturated with one or more double bonds;

R, and R' are independently selected from hydrogen, alkyl, aryl, -OH, -OR", -SH, -SR", -NH_2, -NHR", =O, =NH, =NR";

R" is independently selected from alkyl, aryl,

together with a pharmaceutically acceptable carrier.

7. A method of treating Alzheimer's disease, or a tauopathy (Corticobasal degeneration, Pick's disease, supranuclear palsy, etc), bipolar disorder, diabetes type II, hyperproliferative disease such as cancer, displasais or metaplasias of tissue, psoriasis, arteriosclerosis or restenosis, or chronic inflammatory process, which comprises administering a compound of formula:



FORMULA I

where:

n is 0, 1, 2, or 3

the bonds shown with the dashed lines are saturated, or unsaturated with one or more double bonds;

R, and R' are independently selected from hydrogen, alkyl, aryl, -OH, -OR", -SH, -SR", -NH_2, -NHR", =O, =NH, =NR";

R" is independently selected from alkyl, aryl.